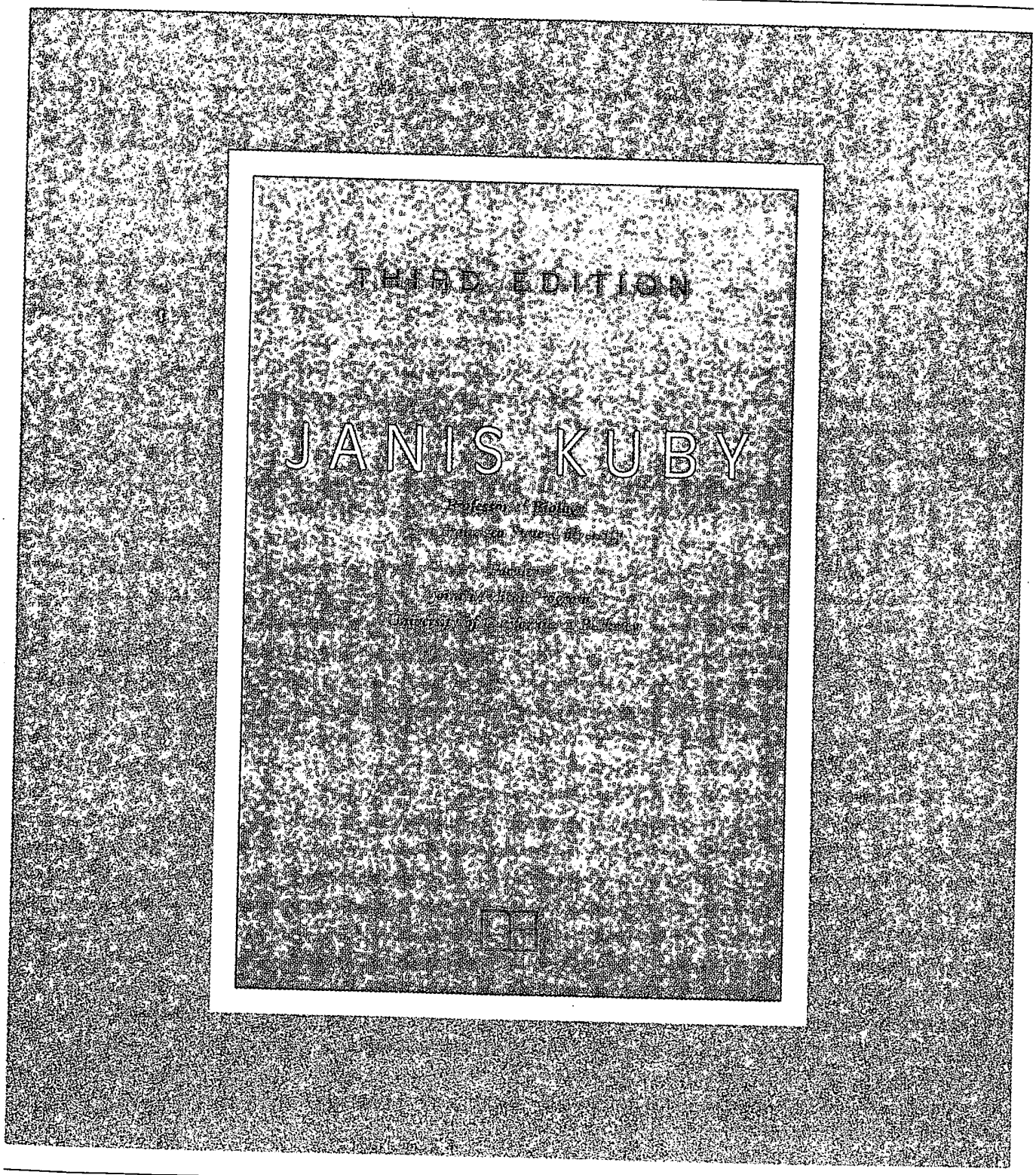
IMMUNOLOGY



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ABOUT THE COVER AND FRONTISPIECE

Interactions of cell adhesion molecules, with different ones involved at different times, are responsible for recruiting leukocytes to inflammatory sites and for their migration through the vascular endothelium. Slowed by vasodilation, leukocytes drift against vessel walls, where selectins are responsible for a loose adherence known as "rolling." This initial step in leukocyte migration is shown in a false-color scanning electron micrograph. (See Chapter 15 for more information.)

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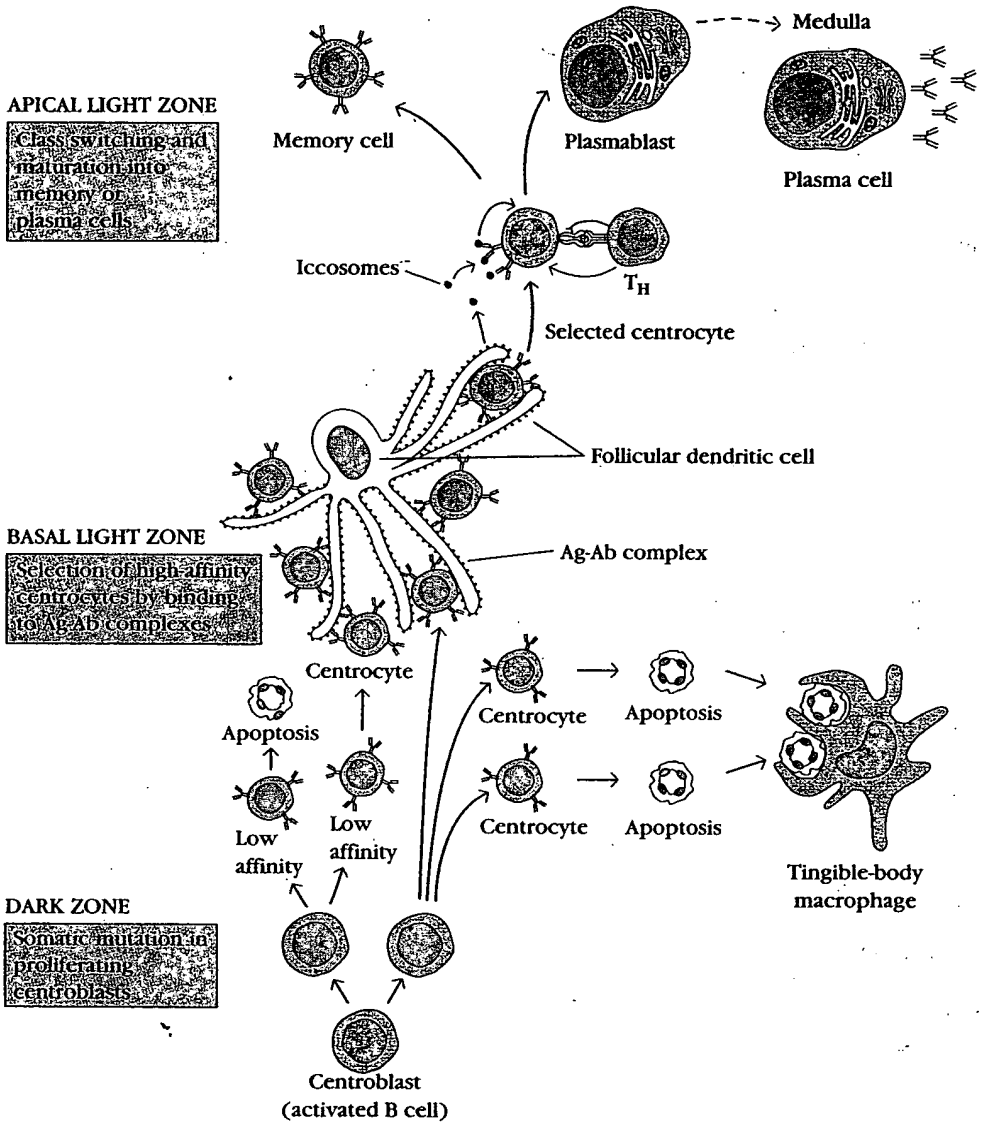

FIGURE 8-16

Overview of cellular events within secondary follicles of peripheral lymph nodes. Follicular dendritic cells bind antigen-antibody complexes along their long processes. Small B cells (centrocytes) bearing high-affinity membrane immunoglobulin (mIg antibodies shown in blue) are thought to interact with antigen presented on the follicular dendritic cells; unselected centrocytes bearing low-affinity mIg die by apoptosis and the debris is phagocytosed by tingible-body macrophages. Selected centrocytes, which may undergo class switching, then mature into memory B cells or plasmablasts; the latter migrate to the medulla where they develop into plasma cells.

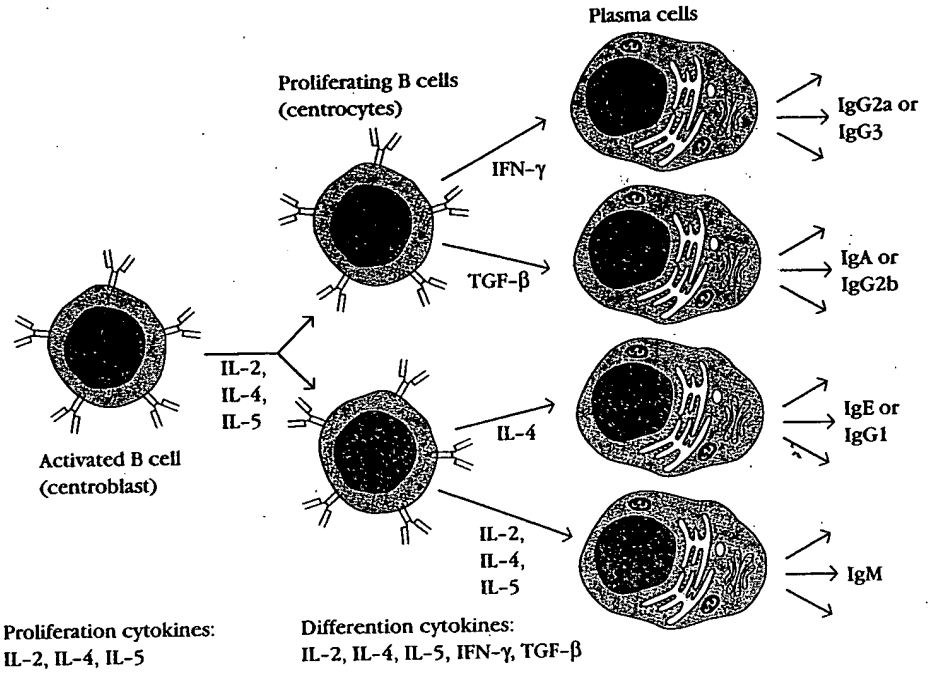

FIGURE 8-19

Numerous cytokines participate in B-cell proliferation and class switching during differentiation into plasma cells. Binding of the proliferation cytokines, which are released by activated T_H cells, provide the progression signal needed for proliferation of activated B cells. The indicated cytokine effects have been demonstrated; however, similar or identical effects may be mediated by other cytokines. Class switching in the response to thymus-dependent antigens also requires the CD40/CD40L interaction, which is not indicated here.

on the action of specific cytokines (Figure 8-19). Cytokines induce class switching by making the switch sites that lie 5′ to each C_H gene accessible, so that switch recombinase enzymes can bind to the site (see Figure 7-12). Exposure of activated B cells to IL-4, for example, results in DNA transcription upstream from the switch regions for $C_\gamma 1$ or C_ε, indicating that the chromatin at these switch sites is now accessible.

In the humoral response to type 1 thymus-independent (TI-1) antigens, class switching does not occur. In the response to TI-2 antigens, class switching to other isotypes can occur, although IgM is the predominant isotype produced. Several cytokines, notably IL-4, IFN-γ, and TGF-β have been shown to be required for class switching in the response to TI-2 antigens. These cytokines are produced by T_H cells, but they can also be produced by other cells enabling class switching during the response to TI-2 antigens even in the absence of T_H cells. Natural killer cells, for example, secrete both IL-4 and IFN-γ, and macrophages and B cells secrete TGF-β.

Class switching is also influenced by the microenvironment of the plasma cell. Plasma cells leaving the follicles of Peyer's patches or mesenteric lymph nodes are almost all committed to IgA production. In contrast, plasma cells originating in the tonsils, spleen, or peripheral lymph nodes are mainly committed to IgG production.

Generation of Plasma Cells and Memory B Cells

Following selection of centrocytes bearing high-affinity mIg for antigen displayed on follicular dendritic cells, the centrocytes differentiate into plasma cells and memory B cells in the apical light zone (see Figure 8-16). It appears that different membrane signals may determine whether a plasma cell or a memory cell is formed, as depicted in Figure 8-20.

Formation of plasma cells is thought to be induced by IL-1 and CD23, which are produced by follicular dendritic cells. CD23 is expressed in a membrane form and is also released in a soluble form, which acts in a paracrine fashion on nearby centrocytes. As noted earlier, CD23 is a ligand for the CR2 component of the coreceptor complex on the B cell. The interaction of either membrane or soluble CD23 with CR2 on the B cell, together with an IL-1 signal, induces the centrocyte to differentiate into a plasma cell.

Plasma cells generally lack detectable membrane-bound immunoglobulin and instead synthesize high levels of secreted antibody. Differentiation of mature B cells into plasma cells must involve a change in RNA processing so that the secreted form of the heavy chain rather than the membrane form is synthesized (see